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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

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DETAILED ACTION

ADVISORY ACTION

This Office Action is in response to Applicant's arguments filed 06 July 2010.

11.

Rejections Maintained

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Katsukiyo et al. (US Patent No. 5,733,892, cited in previous Office Action) in view of Shigehisa et al. (JP 06-072893, cited in previous Office Action).

Katsukiyo et al. teaches compounds prepared by linking glycosaminoglycan to phospholipid or lipid (abstract). Examples 4 and 5 provide for the preparation of L-(α-phosphatidyl)ethanolamine dipalmitoyl-linked glycosaminoglycans (GAG-PPEADP). Specifically, Lot No. 1000 provides for the compound HA1-PPEADP (columns 47-50, tables L and M). Katsukiyo teaches their use as metastasis inhibitors (claim 1).

Katsukiyo et al. teaches the contents of phospholipid or lipid portions in the phospholipid- or lipid-linked glycosaminoglycans represented by formula (VIII) may range from 0.005 to 50% (column 34 lines 40-44). Applicant's disclosure of hydrogel includes the use of 1 to 100 equivalents of phosphatidyl ethanolamine based on 100 equivalents of the carboxyl group of hyaluronic acid (specification, column 6 lines 22-35 and column 7 lines 1-13). The range presented by Katsukiyo et al. is within the range provided in the disclosure.

Katsukiyo et al. also teaches the injectable solutions of the salt forms of the phospholipid- or lipid-linked glycosaminoglycan (column 35, lines 1-3). A syringe containing said injectable solution can be considered as a molded form of hyaluronic acid.

Katsukiyo et al. does not expressly disclose the embodiment of phosphatidyl ethanolamine where the acyl groups are unsaturated.

Shigehisa et al. teaches an antirheumatic compound which uses lipid conjugates of glycosaminoglycans or its salts

Shigehisa et al. teaches that lipid-binding GAG weakens the inflammation of synovial tissue, i.e. the lipid-binding GAG reduces the neoplasia (metastasis) of a

synovial cell, fibrin deposition, the coagulation of lymphocytes, as well as prevent the extension of pannus involved in rheumatism (paragraph 0100). Shigehisa et al. teaches the binding of the carboxylic acid functional group of uronic acid in a glycosaminoglycan with the amine group of a lipid (paragraph 0016, chemical formula 1, C). Shigehisa et al. also teaches that the glycosaminoglycan used can be hyaluronic acid (paragraph 0020) and that the chain length and degree of unsaturation of an acyl group in a lipid are not limited (paragraph 0021). Shigehisa et al. teaches that phospholipid modified GAGs can be administered by intraarticular injection as well as various other forms of administration to the synovial cavity, i.e. joints (paragraphs 0057, 0059, 0066). Shigehisa et al. teaches administering the GAGs to mice (paragraph 0065).

It would have been obvious at the time the invention was made to modify the 6-position of hyaluronic acid with dioleoylphosphatidyl ethanolamine and to administer this compound into the joint of a patient.

MPEP 2141 states, "The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in KSR noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit. The Court quoting In re Kahn, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006), stated that "[R]ejections on obviousness cannot be sustained by mere conclusatory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.'" KSR, 550 U.S. at, 82 USPQ2d at 1396. Exemplary rationales that may support a conclusion of obviousness include: (A) Combining prior art

elements according to known methods to yield predictable results; (B) Simple substitution of one known element for another to obtain predictable results; (C) Use of known technique to improve similar devices (methods, or products) in the same way; (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; (E) " Obvious to try " choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention."

Based on the teachings of the MPEP and KSR above, by employing the rationale in (B) simple substitution of one known element for another to obtain predictable results and (G) some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention; one having ordinary skill in the art would have been motivated to modify the 6-position of hyaluronic acid with dioleoylphosphatidyl ethanolamine and to administer this compound into the joint of a patient. Both Katsukiyo et al. and Shigehisa et al. teach that phospholipid modified glycosaminoglycans are useful in inhibiting metastasis. In addition to generally inhibiting metastasis, Shigehisa et al. teaches that phospholipid modified

glycosaminoglycans can specifically inhibit metastasis (neoplasia) in the synovial cavity of joints and treat conditions such as rheumatoid arthritis. Therefore, because the phospholipid modified GAGs taught by Shigehisa et al. is used for similar purpose as that taught by Katsukiyo et al., one having ordinary skill in the art would have been motivated to substite dipalmitoylphosphatidyl ethanolamine for dioleoylphosphatidyl and would predict that this substitution would result in a the instantly claimed compound that should also be suitable for administration into joint.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Response to Arguments

Applicant's arguments filed 06 July 2010 have been fully considered but they are not persuasive.

Applicants main arguments are that the injectable preparation of the hyaluronic acid hydrogel is merely described "as one of a large number of dosing preparations enumerated in Katsukiyo" (p.2, remarks, second paragraph). And Applicant has argued that the instantly claimed compound must have a high elastic modulus (must be able to be administered) when it is prepared as a hydrogel and that both Katsukiyo and Shigehisa fail to disclose or suggest the hyaluronic acid compound and a joint protection function.

Hyaluronic acid as a therapeutic compound is well known in the art, and as a result many different formulations and preparations have been described in the past.

However, Katuskiyo does not provide a laundry list of various dosages but rather provides specific formulations for when the compound is administered as a solid, an injectable solution, a suppository and as a topical treatment (see column 35, lines 29-38). The recitation of four different concentration ranges can hardly be seen as a "large number of dosing preparations". It should also be noted that mice were actually injected with the compounds (see column 35, lines 52-67), therefore even though it is not necessary for the compound to have actually been injected since the art teaches how to inject them, Katsukiyo has demonstrated that it has been successfully performed.

The instant claims are drawn to substitution of phosphatidyl ethanolamine that is conjugated to hyaluronic acid, with an unsaturated C18 fatty acid, i.e. oleic acid. Katsukiyo et al. specifically describes a saturated C16 fatty acid, i.e. palmitic acid and a saturated C18 fatty acid, i.e. stearic acid. Therefore, the only difference between the hyaluronate phosphilipids actually embodied by Katsukiyo et al. and the instant claims are one unsaturated bond. Shighesa et al. teaches that the phospholipids can be saturated or unsaturated, therefore one could readily envisage substituting stearic acid for oleic acid. Because of the close structural similarity, one of ordinary skill in the art would expect substitution of one for the other would result in a compound having similar properties. Shigehisa et al. resolves the deficiencies of Katsukiyo wherein the reference suggests to one of ordinary skill that these hyaluronates can be used in various applications including administration into joints, wherein the hyaluronate can be modified with various phospholipids having unlimited chain length and unsaturation.

Since it is clear that the compounds having extremely close structural similarity to that instantly claimed, it is clear that they have a high elastic modulus when prepared as a hydrogel. And the prior art reference as a whole does in fact suggest the instantly claimed compound for administration into the joint. It is not necessary that the prior art reference have the same intended use as applicants, i.e. joint protection function since this treatment (result) will occur upon administration of the compounds taught by the prior art as a whole. Shigehisa et al. suggests administering this class of compounds directly into the synovial cavity, which includes joints such as the knee.

The rejection is hereby **maintained**.

Conclusion

In view of the rejections to the pending claims set forth above, no claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ms. BAHAR SCHMIDTMANN whose telephone number is 571-270-1326. The examiner can normally be reached on Mon-Thurs 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ms. Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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